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Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

STATISTICAL KEY WORS : cross-over, equivalent trial

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3. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

3.1 Conclusion and Recommendations

In Study 0018, the primary endpoint of efficacy was the rate of severe hematuria, and the two regimens (mesna injection and mesna tablets) were to be considered equivalent if the upper bound of two-sided 95% confidence interval of the difference between the two treatment arms were ≤ 10%. One incidence of hematuria occurred in each of two mesna regimens. The upper bounds of two-sided 95% confidence interval using the first cycle data only were 29.1% and 20.3% for intent-to-treat (ITT) population and per-protocol (PP) population, respectively, and the upper bounds of two-sided 95% confidence interval of crossover comparison using both cycles were 7.6% and 2.3% for ITT population and PP population, respectively. Although the upper bounds from crossover comparison were lower than the pre-defined equivalence margin of 10%, crossover comparison may be biased due to high dropout rate at the second cycle of the study. Explanation in detail can be found in Section 4.3.2, page 10.

In Study 3126, one incidence of hematuria was found from each mesna regimen. This trial was conducted to younger patients compared to Study 0018

Due to small sample size and high dropout rate at the second cycle of the study, the statistical evidence submitted in this NDA is not sufficient to support equivalence between two mesna regimens. The equivalence of the efficacy should be based on clinical and PK/PD judgement.

3.2 Overview of the Clinical Program and Studies Reviewed

Mesna is a thiol compound that exerts a detoxifying action against the urotoxic metabolites of ifofamide, resulting in a lower incidence of hemorrhagic cystitis than that seen when ifosfamide is administered alone. Mesna injection was approved for the prevention of ifosfamide-induced hemorrhagic cystitis in 1988. In 1997, an NDA was submitted for the approval of mesna tablets for the same indication as mesna injection in an iv plus oral dosing regimen where the last two of the three iv doses would be replaced by oral doses. This NDA was not approved due to its inadequacy. In 2001, an amendment to the NDA was submitted with re-analysis of one pivotal trial conducted in U.S., D-07093-0018, and a final analysis of new phase II pharmacokinetic study (Study D-07093-3126). Study 0018 was re-analyzed by this reviewer for efficacy claim of mesna tablets, and Study 3126 was reviewed for supportive evidence.

Study 0018 is open label, randomized, two-way crossover trial comparing iv and iv/oral regimen of mesna in patients treated with ifosfamide. The patients were randomized so that in one cycle patients received the standard iv treatment (iv), and in the other cycle patients received the iv plus oral dosing regimen (iv+po). Then the patients were switched over to the other mesna regimen in the second treatment cycle.

28 patients in the study were assigned to treatment sequence iv+po/iv, and 30 patients were assigned to treatment sequence iv/iv+po according to a randomization schedule.

Study 3126 is multi-center, open-label, randomized, multiple-dose, two-way crossover Phase II pharmacokinetic evaluation of the treatment iv+po/iv vs. iv/iv+po regimens in sarcoma patients treated with ifosfamide. 10 patients were assigned to treatment sequence iv+po/iv, and 8 patients were assigned to treatment sequence iv/iv+po according to the randomization schedule.

The following table summarizes the design and sample size of Study 0018 and Study 3126.

Table 1. Design and Sample Size of Study 0018 and Study 3126

Study	Treatment Sequence	Cycle 1	Cycle 2	Number of Patients
Study 0018	Sequence I	IV+PO	IV	28
	Sequence II	IV	IV+PO	30
Study 3126	Sequence I	IV+PO	IV	10
	Sequence II	IV	IV+PO	8

In Study 0018, two analyses were performed by the sponsor; parallel comparison for ITT population using the first cycle data only, and crossover comparison for PP population using both of the cycles. Test results from parallel comparison did not meet the equivalence margin of 10%, but the analyses of PP population provided the narrower confidence interval of the two mesna regimens. This reviewer's analyses confirmed the sponsor's results.

In Study 3126, no statistical analysis for efficacy endpoint was performed by the sponsor since the trial was not designed to show the equivalence of efficacy of two regimens. However, the incidence of hematuria was monitored as safety parameter, and this parameter was examined for the supportive evidence by this reviewer.

3.3 Principal Findings

There were a couple of points that were not correctly considered when the sponsor re-analyzed Study 0018. One was using **one-sided** 95% confidence bound when using **two-sided** 95% confidence bound was required. The other point was mishandling dropouts. About 15% of patients prematurely dropped out of the study, and these dropouts were considered as **success** from the treatment by the sponsor. This analysis could mislead the conclusion, especially when significant number of patients prematurely discontinued from the trial. In this study, the number of prematurely discontinued patients was larger than the number of patients with hematuria (nine dropouts vs. two incidence of hematuria). Therefore, the results of sponsor's analyses have a great potential of being biased.

As a sensitivity analysis, this reviewer calculated **two-sided** 95% confidence bounds with counting dropouts as **failures**. The upper confidence bounds for ITT population and PP population using the first cycle only (parallel comparison) were 29.1% and 20.3%, respectively, and the upper confidence bounds for ITT population and PP population using both cycles (crossover comparison) were 7.6% and 2.3%, respectively. The upper 95% confidence bound of crossover comparison meets the equivalence margin of 10%, however, the results may be biased due to the high dropout rate (15%) in the study.

In Study 3126, two incidences of hematuria occurred; one incidence for each of two mesna regimens. Statistical test was not performed since this trial was not designed to conduct efficacy tests, and the sample size was too small to test a hypothesis and draw a conclusion.

4. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

4.1 Introduction and Background

Mesnex (generic name, mesna) Injection was approved in the US in 1988 as a prophylactic agent to prevent the hemorrhagic cystitis induced by ifosfamide. Urothelial toxicity of ifosfamide is related to the ifosfamide dose and presents as hemorrhagic cystitis, dysuria, polyuria, microhematuria, macrohematuria and other symptoms of bladder irritation. The pathogenesis of the ifosfamide-induced urinary bladder lesions indicates a primary damage at the luminal membrane of the epithelial cells. Subsequently, the epithelial bladder cells are destroyed, intermediary cells, basilar cells, capillaries, and venules are damaged, and deeper layers of the bladder wall are no longer protected against secondary damage by hypertonic urine and urotoxic metabolites of ifosfamide. Macrohematuria and massive bleeding result from severe lesions of deeper layers of the baldder wall. Microhematuria and macrohematuria have been used as indicators of ifosfamide-induced bladder wall lesions. The extent of hematuria might reflect the extent of the lesions. The approved schedule for Mesnex Injection is three intravenous doses at 0, 4, 8 hours relative to ifosfamide administration; each mesna dose is equivalent to 20% of the corresponding ifosfamide dose. This multiple dose regimen is required because the half-life for excretion of mesna is shorter than that of ifosfamide. The approved mesna regimen requires that patients treated in hospital or outpatient settings remain in the clinic for more than 8 hours. To improve the quality of care for patients given ifosfamide, ASTA Medica initiated a program to develop oral formulations of mesna. The oral administration of mesna by drinking ampules or injection solution is effective but the bad taste and unpleasant odor jeopardize reliable compliance. For this reason, mesna film-coated tablets were developed. Mesna tablets will be used for the same indication as Mesnex Injection in an iv plus oral (iv+po) dosing regimen where the last two of the three iv doses will be replaced by oral doses.

In 1997 the NDA was submitted to seek the approval of mesna tablets for the same indication as mesna injection. In the NDA two open, randomized, multicenter controlled trials, Study D-07093-0018 (US study) and study MED504 (German study), were reported. Study D-07093-0018 was a two-way crossover trial, and Study MED504 was a parallel group study comparing the treatment iv with iv+po. In addition, the Vanderbilt study (D-07093-0019), primarily a pharmacokinetic study, was also treated as a controlled study in the NDA. The review was focused on the two pivotal trials, D-07093-0018 and MED504, for efficacy claims. As a result of the review, the application was not approved due to its inadequacy. The deficiencies may be summarized as follows:

1. Serious deficiencies in the monitoring of the controlled U.S. study (D-07093-0018) had been identified by FDA's Division of Scientific Investigation (DSI). These new findings call into question the validity of the study results, which provided the critical urinary pharmacokinetic data upon which bioequivalence was based and also provided important safety information.

2. The findings from the controlled U.S. study (D-07093-0018) did not achieve statistical equivalence when the data were re-analyzed using only first cycle data and excluding 12 patients from Center 5 (C. Julian Rosenthal) and 5 patients who discontinued from study prematurely.

In August 2001, the sponsor submitted NDA amendment to seek the approval with re-analysis of Study 0018, and a final study reports of new phase II pharmacokinetic study.

4.2 Data Analyzed and Sources

The NDA contains the final study report for the re-analysis of the efficacy and safety trial D-07093-0018, excluding the data from study center 5. The study is open label, randomized, two-way crossover trial comparing treatment iv+po/iv vs. iv/iv+po regimens. 28 patients in the study were assigned to treatment sequence iv+po/iv, and 30 patients were assigned to treatment sequence iv/iv+po according to the randomization schedule. In addition, the NDA amendment contains final study reports for the randomized trial d-07093-3126, a Phase II pharmacokinetic evaluation of the treatment iv+po/iv vs. iv/iv+po regimens in sarcoma patients treated with ifosfamide. This study is multi-center, open label, randomized, multiple dose, two-way crossover trial. 10 patients were assigned to treatment sequence iv+po/iv, and 8 patients were assigned to treatment sequence iv/iv+po according to the randomization schedule.

4.3 Statistical Evaluation of Evidence of Efficacy/Safety of Study 0018

4.3.1 Detailed Description of Study 0018

The primary endpoint was the rate of severe microhematuria (Grade III) and macrohematuria (Grade IV). This endpoint was assessed by counting RBCs/hpf and by examining the urine for visible blood. The incidence of hematuria was summarized for each mesna regimen using the classification scheme that was shown in the Table 2.

Table 2 : Classification of Blood Counts

Counts (RBCs/hpf)	Grade
0-20	Grade I
21-50	Grade II
> 50	Grade III
Visible blood	Grade IV

The patients in iv treatment cycle received the mesna injection on all 5 treatment days concurrently with ifosfamide (0h), and at 4h and 8h. The dose for each iv administration was calculated as 20% of the daily ifosfamide dose. The patients in iv+po treatment cycle received the mesna tablets on all 5 treatment days of the cycle at 2h and 6h after start of the ifosfamide infusion. The dose for each po administration was approximately 40% of the daily ifosfamide dose. The following table shows the treatment schedule and the dose of mesna related to the ifosfamide dose.

Table 3: Treatment Schedule of Study 0018

Treatment Arm	Mesna Dose as Percentage of Ifosfamide Dose				
	0 h	2 h	4 h	6 h	8 h
IV	20% iv		20% iv		20% iv
IV+PO	20% iv	40% po		40% po	

An upper 95% confidence bound was estimated based on the normal approximation of the absolute difference $D=P_1 - P_2$ where P_1 and P_2 are the proportions of observing a severe microhematuria or macrohematuria (visible blood) with the iv+po and iv regimens, respectively. The two regimens were to be considered equivalent if the upper 95% confidence bound was $\leq$ 10%. The analysis was to be performed for both intent-to-treat (ITT) population and per-protocol (PP) population. The ITT population consisted of all patients who received at least one dose of mesna. The PP population consisted all patients who were evaluable for hematuria. An analysis of carryover effects was planned in the protocol; however, the test was not performed due to the low rates of severe microhematuria and macrohematuria observed. The total number of evaluable patients planned in the protocol was 120. However, only 71 patients were recruited and randomized to treatment with sequence 1 (Mesna iv+po/iv; n=34) or with sequence 2 (Mesna iv/iv+po; n=37). 13 patients from Center 5 were excluded from the analysis since data collected from the center were inadequate according to the FDA's audit of the study centers. 9 patients from each treatment group were excluded from per-protocol population due to early dropouts or

major protocol violations. The following table provides a brief overview on the study population and disposition:

Table 4. Disposition of Patients in Study 0018

	N of Patients		
	IV+PO/IV	IV/IV+PO	Total
Patients randomized	34	37	71
Safety population	34	37	71
Center 5 not evaluated for efficacy	-6	-7	-13
ITT population	28	30	58
Major protocol violations	-9	-9	-18
PP population	19	21	40

4.3.2 Study 0018: Sponsor's Results and Conclusions

Baseline demographic characteristics of patients are summarized in the following table.

Table 5: Summary of Baseline Demographic Characteristics of Study 0018

Parameter		Treatment Sequence	
		IV+PO/IV	IV/IV+PO
		N=34	N=37
Sex	Male	16 (47%)	19 (51%)
	Female	18 (53%)	18 (49%)
Race	White	28 (82%)	31 (84%)
	Black	4 (12%0	4 (11%)
	Hispanic	1 (3%)	2 (5%)
	Asian	1 (3%)	0 (0%)
Age (years)	Mean	55.6	59.2
	SD	15.7	12.5
	Range	23-80	31-77
Weight (kg)	Mean	69.0	70.7
	SD	17.9	18.7
	Range	40-107	37-112
Performance Status (ECOG)	0	18	21
	1	13	14
	2	2	0
	missing	1	2

As shown in the table, there was no statistically significant difference between two treatment arms.

During the trial, more than 15% of the patients were prematurely discontinued from the study. Due to this loss of subjects in the second cycle of the study, the analyses based on the crossover data may not be valid. With so many missing subjects, the major issue of such analyses was as pointed out in the ICH guideline that "There are additional problems that need careful attention in the crossover trials. The most notable of theses are the complications of analysis and interpretation arising from the loss of subjects." Since most patients completed the first cycle, FDA previously recommended conducting the statistical analysis based on the first cycle data only (using parallel comparison). The sponsor's analysis results are summarized in the following table.

Table 6: Sponsor's Result : ITT Population – Parallel Comparison

Incidence of Grade III or IV Hematuria in first cycle			95% upper C.I.
IV+PO	IV	Difference	one-sided
*1/28=3.6%	0/30=0.0%	3.6%	12.8%

*patient 3/7 : This patient had a history of bladder cancer and hematuria and was entered in the study in violation of the protocol. He was withdrawn from the study after the iv+po cycle and died of pneumonia and progressive disease, 21 days later.

The sponsor conducted crossover comparison for PP population using data from both cycles. The data from the second cycle could be biased due to high rate of dropouts. The following table shows the results of the test.

Table 7: Sponsor's Result : PP Population – Crossover Comparison

Incidence of Grade III or IV hematuria			95% upper C.I.
IV+PO	IV	Difference	one-sided
*1/40=2.5%	#1/40=2.5%	0.0%	5.8%

*patient 3/7

patient 6/8 : this patient had Grade I hematuria in the first (iv+po) cycle, and Grade III in the second (iv) cycle.

The upper confidence bound from ITT population was 12.8%, which was higher than the pre-specified equivalence margin of 10%, and the upper confidence bound from PP population was 5.8%. However, the results may be biased due to high dropout rates.

There were a couple of points that were not correctly considered by the sponsor. First of all, as previously suggested by the FDA, and as clearly stated in the ICH guideline that "For equivalence trials, two-sided confidence intervals should be used", two-sided confidence intervals had to be used instead of the one-sided confidence interval. The second problem with the sponsor's analyses was the method of handling the dropouts. When rates of incidence of hematuria were computed, only the patients experiencing hematuria were counted as failure from the treatment, and prematurely discontinued patients were not handled in any way. By doing so, dropouts were considered success from the treatment since the number of prematurely discontinued

patients was included in denominator. Since prematurely discontinued patients tend to show no response to the treatment, this practice can misled to the equivalence.

4.3.3 Statistical Methodologies of Study 0018

The response rates from the parallel design, where patients are randomized to one of the two treatments and were treated with one treatment only, are independent- the patients in one treatment are different from the other treatment. However, the response rates from the crossover design are dependent since the patients are crossed over to the other treatment at the second cycle, so the patients in the second cycle are the patients who are previously treated with the other treatment in the first cycle. Therefore, two different methods for calculating confidence interval for the difference between response rates are used in the analyses. For the parallel comparison using the first cycle only, confidence interval is computed by the methods suggested by [1]Fleiss which used Yates continuity correction. For crossover comparison, method introduced by [2]Agresti is used to compute the confidence interval for the difference between two dependent proportions.

4.3.4 Statistical Reviewer's Findings of Study 0018

As stated in section 4.3.2, the two-sided 95% confidence interval, instead of one-sided, should be used in this study, and the dropouts need to be carefully handled. The following table shows the number of dropouts and the incidence of hematuria in each treatment and each cycle.

Table 8. Number of Dropout and Incidence of Hematuria in Study 0018

Treatment Schedule	Number of Dropouts	Incidence of Hematuria	Total # of Failure
IV+PO/IV			
First cycle (iv+po)	4	1	5
Second cycle (iv)	1	1	2+5 (from 1st cycle)
IV/IV+PO			
First cycle (iv)	3	0	3
Second cycle (iv+po)	1	0	1+3 (from 1st cycle)

As shown in the table, the number of dropouts is larger than the number of hematuria. These numbers show that the final analysis results of this study could be affected by whether the dropouts are counted as failure or not.

Unlike the case in superiority trials, use of the full analysis set, ITT population, is generally not conservative and its role should be considered very carefully in the equivalence or non-inferiority trial. As stated in ICH guideline, subjects who withdraw or drop out of the treatment group tend to have a lack of response; hence

[1] J.L. Fleiss, Statistical methods for rates and proportions 2nd edition (1981), Wiley, pp.29
[2] Agresti A, Categorical Data Analysis John Wiley & Sons, New York 1990, pp 349

the results of using ITT population may be biased toward demonstrating equivalence. Therefore, analysis results from PP population are important as much as results from ITT population in equivalence trial especially when many dropouts are present. Thus, this reviewer analyzed using four different analysis sets; the first cycle of ITT and PP population, and both cycles of ITT and PP population. The following tables (Table 9 and Table 10) show the number of incidence (hematuria and dropout) in the each analysis set with both cycles.

Table 9 : Summary of ITT Population with Crossover Data in Study 0018

		IV+PO treatment		
		Incidence	No incidence	Total
IV Tretments	Incidence	8	2	10
	No incidence	1	47	48
Total		9	49	58

Table 10: Summary of PP Population with Crossover Data in Study 0018

		IV+PO treatment		
		Incidence	No incidence	Total
IV Tretments	Incidence	1	1	2
	No incidence	0	38	38
Total		1	39	40

Table 11 shows the two-sided upper confidence bound for ITT and PP populations for both parallel comparison and crossover comparison.

Table 11: The Reviewer's Analysis Results of Study 0018

Cycles	Population	Difference	Two-sided 95% upper Confidence bound
1st cycle only (parallel)	ITT	7.9%	29.1%
	PP	5.3%	20.3%
Both cycles (cross-over)	ITT	1.7%	7.6%
	PP	-2.5%	2.3%

As shown in the above table, there existed a difference between the upper 95% confidence bounds of parallel comparison and crossover comparison. While the upper 95% confidence bounds of parallel comparison were higher than the pre-defined equivalence margin of 10%, the upper 95% confidence bound of crossover comparison met the equivalence margin. However, the results from crossover comparison should be carefully interpreted because of the high dropout rate in the second cycle. The sample sizes of both comparisons were not appropriate to achieve a suitable power.

4.4 Statistical Evidence of Evidence of Efficacy and Safety of Study 3126

4.4.1 Detailed Description of Study 3126

Study 3126 was Phase II Parmacokinetic multicenter, open label, randomized, multiple dose, crossover trial. Sarcoma patients scheduled for treatment with a 5-day schedule of ifosfamide and mesna were randomly allocated to receive in the first treatment cycle (A) all mesna doses as intravenous infusion or (B) only the first mesna dose of the day as an intravenous infusion and the subsequent daily doses as tablets. In the second treatment cycle patients changed over to the other dosing scheme for mesna. The second cycle had to follow the first cycle within 3-8 weeks, allowing for recovery from toxicity of the cytostatic treatment. Each cycle consisted of 5 consecutive days during which ifosfamide was administered once daily with a dose of 2.0 g/m^2. The dose of mesna was adjusted in relation to the ifosfamide dose. Table 12 shows the treatment schedule of mesna regimens.

Table 12: Treatment Schedule of Study 0018

Treatment Arm	Mesna Dose as Percentage of Ifosfamide Dose				
	0 h	2 h	4 h	6 h	8 h
IV	20% iv		20% iv		20% iv
IV+PO	20% iv	40% po		40% po	

In this trial the incidence of hematuria was monitored primarily for safety reason. The incidence of hematuria was summarized for each mesna regimen using the following classification scheme:

Table 13 : Classification of Blood Counts

Erythrocytes in urine sediment		
Counts (cells/hpf)	Verbal classification	Grading
0-20	Negative, none, trace, occasional	Grade I
21-50		Grade II
> 50		Grade III
Too numerous to count	Visible blood, hematuria	Grade IV

All sediment results were used to determine the maximum grade of hematuria per treatment cycle. It was planned to have 12 evaluable patients. A total of 18 patients were randomized, with 17 exposed to at least one dose of study medication. The following table provides a brief overview of disposition of patients.

Table 14: Disposition of Patients of Study 3126

	N of Patients		
	IV+PO/IV	IV/IV+PO	Total
Screened	10	8	18
Randomized	10	8	18
Not exposed	-1	-	-1
Safety population	9	8	17
Major protocol violation	-2	-2	-4
PP	7	6	13

Among four patients with major protocol violation, three patients were prematurely discontinued, and one patient had a condition that interfere with absorption of mesna due to resection of stomach. The following table summarizes the main demographic data of Study 3126.

Table 15: Baseline Demographic Characteristics of Study 3126

Parameter		Treatment Sequence	
		Iv+po/iv	Iv/iv+po
		N=9	N=8
Sex	Male	2	5
	Female	7	3
Race	White	9	7
	Black	0	1
Age (years)	Mean	39.3	47.4
	SD	10.2	20.0
	Range	25-57	19-74
Weight (Kg)	Mean	71.6	76.4
	SD	20.9	18.6
	Range	52-117	52-99

As shown in the above table, 2 (22%) patients were male and 7 (78%) patients were female in iv+po/iv arm while 5 (62.5%) patients were male and 3 (37.5%) patients were female. The table also showed that the patients in iv+po/iv arm were younger than the patients in iv/iv+po arm.

4.4.2 Sponsor's Results and Conclusions of Study 3126

The following table summarizes the crossover comparison of results for the mesna schedules.

Table 16 : Crossover Comparison of Study 3126

		N of Patients					
		IV Treatment					
		Hematuria Grade					
	Hematuria Grade	I	II	III	IV	Missing	Total
IV+PO Treat-ment	I	9	1	0	1	1	12
	II	2	1	0	0	0	3
	III	1	0	0	0	0	1
	IV	0	0	0	0	0	0
	Missing	1	0	0	0	0	1
	Total	13	2	0	1	1	17

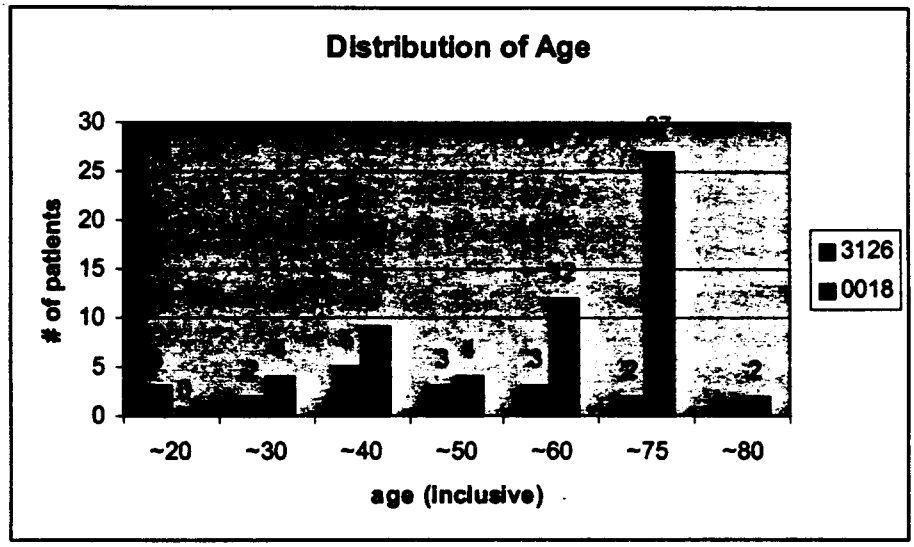
Including data from both treatment sequences, there was one patient who showed a macroscopically visible hematuria (Grade IV). This patient (patient 3/8) suffered hematuria on day 6 of the first treatment cycle during which mesna had been given by iv injection. In the second treatment cycle, when mesna was given in the combined iv+po dosing scheme, urinalysis showed only minimal (Grade I) findings. One patient had Grade III hematuria. This patient (patient 1/6) suffered hematuria on day 2 of the first cycle, when mesna was given in the combined iv+po dosing scheme. The patient, however, showed Grade I hematuria in the second treatment cycle during which mesna had been given by iv injections.

These results support the assumption that the more feasible dosing scheme with the oral dosing provided similar uroprotection as the dosing scheme in which all mesna doses are given by intravenous injection. No statistical test was performed since only limited information regarding the relative uroprotective efficacy can be derived from the safety parameter in the trial due to the limited number of patients and the crossover design.

4.4.3 Statistical Reviewer's Findings in Study 3126

The demographic background of patients from Study 3126 was compared with the demographic background of patients of pivotal trial, Study 0018. All demographic background of patients between two studies were similar except age. The mean of the age of patients from Study 0018 was 57.5 while the mean of the age of patients from Study 3126 was only 41.4. Even the inclusion criteria for age between two trials were somewhat different. In Study 0018, the age of the patient was set to be greater or equal to 18 while the age of the patient had to be between 18 and 75, inclusive, in Study 3126. The following bar graph shows the distribution of the patients' age from two studies.

Figure 1 : Comparison of Age of Patients between Study 0018 and Study 3126



As the graph showed, 50% (29/58) of patients were 61 or older in Study 0018 when only 11% (2/18) of patients were in the same rage in Study 3126. And 56% (10/18) of patients in Study 3126 were less than or equal to 40 years old while only 22% (13/58) of patients in Study 0018 were younger than 41. This suggested that the patients from Study 3126 represented the younger population.

PP population was also examined by this reviewer. Four patients were excluded due to premature discontinuation and major protocol violation; two patients were from iv/iv+po mesna regimen, and the other two patients were from iv+po/iv mesna regimen. Among these four patients, the incidence of hematuria was not detected. As stated in the section 4.4.2, one patient (patient 3/8) had Grade IV hematuria during the first cycle treatment (iv) and Grade I hematuria in the second cycle (iv+po). One more patient (patient 1/6) showed the incidence of hematuria (Grade III) during the first cycle (iv+po), but this patient had hematuria Grade I during the second cycle (iv).

4.5 Statistical Evaluation of Collective Evidence

In Study 0018, four statistical analyses were performed with four different analysis sets; ITT population and PP population with the first cycle only, and ITT population and PP population with the first and the second cycle. The data from the first cycle were used due to relatively high dropout rates in the second cycle. These dropouts were considered as failure of the treatment in this reviewer's analyses. The following table summarizes the results of the four analyses.

Table 17 : The Reviewer's Analysis Results of Study 0018

Cycles	Population	Difference	Two-sided 95% upper Confidence bound
1st cycle only (parallel)	ITT	7.9%	29.1%
	PP	5.3%	20.3%
Both cycles (cross-over)	ITT	1.7%	7.6%
	PP	-2.5%	2.3%

The broad confidence interval of parallel comparison may come from small sample size. The sample size of crossover comparison were about a half of planned sample size, which was 120, and the sample size of parallel comparison was about a half of the sample size of crossover comparison.

In Study 3126, the incidence of hematuria was monitored as the safety parameter. Since this trial was not designed to show efficacy, and was not powered to show equivalence between two mesna regimens, no test was performed from this trial. Instead this trial was reviewed by counting the number of incidence of hematuria from each mesna regimen only for supportive evidence of efficacy of mesna tablets. There was one incidence of hematuria from each mesna regimen. One patient had Grade III hematuria during the first cycle, when mesna was given in the combined iv/po dosing scheme, and the other patient had Grade IV hematuria during mesna had been given by triple iv injection. The following table summarizes the incidence of hematuria in Study 3126

Table 18 : Incidence of hematuria in Study 3126

Treatment Schedule	Number of Hematuria
IV+PO/IV	
IV+PO (first cycle)	1
IV (second cycle)	0
IV/IV+PO	
IV (first cycle)	1
IV+PO (second cycle)	0

The demographic background of patients was checked to see whether the patients represented the same population from the pivotal trial, Study 0018. There existed one significant difference between ages of patients. While about half of the patients from Study 0018 were 61 or older, more than half of the patients from Study 3126 were younger than 41.

4.6 Conclusions and Recommendations

In Study 0018, two incidences of hematuria occurred; one incidence in iv injection treatment arm, and one in iv+po treatment arm. The two-sided upper 95% confidence

bounds of parallel comparison were 29.1% and 20.3% for ITT and PP population, respectively. The two-sided 95% upper confidence bound of crossover comparison was 7.6% and 2.3% for ITT population and PP population, respectively. However, these results from crossover comparison may be biased due to high rate of dropout in the study.

Study 3126 was conducted to younger patients compared to Study 0018. In this study, one incidence of hematuria was found from each mesna regimen.

The data from Study 0018 and Study 3126 are not sufficient to show that the mesna iv and iv+po regimens are equally effective in protecting patients from ifosfamide-induced urotoxicity. The evidence of equivalence of the efficacy should be based on clinical and PK/PD judgement.

/S/

Jasmine Choi, M.S.
Mathematical Statistician

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Jasmine Choi
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Gang Chen
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Kooros Mahjoob
2/28/02 10:15:47 AM
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Statistical Review and Evaluation

MAR 3 1998

NDA#:	20-855
Applicant:	ASTA Medica, Inc., Hackensack, New Jersey
Name of Drug:	Mesna Tablets
Indication:	Prevention of Ifosfamide-Induced Hemorrhagic cystitis
Documents Reviewed:	Vol. .1, .58 - .63 of the NDA, Submission dated 3/27/97
Medical Reviewer:	Gerald Sokol M.D.

****

This review consists of four items: the review of the original submission, Addendum #1, Addendum #2 (Vol. B2, submission date: 12/17/97) and the Overall Conclusions of this review. Addendum #1 addresses the influence of the exclusion of 12 patients in Center #5 (inadequate data collection) on the efficacy results. Addendum #2 reviews the sponsor's updated analyses for the mesna NDA submission.

Major Statistical Issues

1. Validity of the cross-over data analyses: Due to the loss of over 15% of patients in the second cycle of the study, the analyses based on the cross-over data may not be valid.

2. Validity of the Wilcoxon test for the RBC counts (details are included in reviewer's Comments on page 7)

I. Background

Mesna is a thiol compound that exerts a detoxifying action against the urotoxic metabolites of ifosfamide, resulting in a lower incidence of hemorrhagic cystitis than that seen when ifosfamide is administered alone. Mesna injection was approved for the prevention of ifosfamide-induced hemorrhagic cystitis in 1988. The purpose of this NDA is to seek approval of Mesna tablets for the same indication as Mesna injection in an iv plus oral dosing regimen where the last two of the three iv doses will be replaced by oral doses. Two open, randomized, multicenter controlled trials, study **D-07093-0018** (MR9205002A, US study) and study **MED504** (German study), are reported. Study D-07093-0018 is an open label randomized two-way crossover trial comparing treatment iv + po/iv vs. iv/iv+po regimens. The patients in the study were as signed to either treatment sequence iv+po/iv or iv/iv+po according to a randomization schedule. Study MED504 is an open-label, randomized parallel group study conducted in

Germany comparing the treatment iv/iv/iv with iv/po/po. In addition, the Vanderbilt study (D-07093-0019), primarily a pharmacokinetic study, was also treated as a controlled study in this NDA. This review will focus on the two pivotal trials, D-07093-0018 and MED504. The results from the two pivotal trials will be evaluated for efficacy claims.

II. Description of Trials

In the German **(MED504)** and the US **(MR9205002A)** studies, incidence of hematuria was used as the primary efficacy endpoint as was the case for the approval of intravenous Mesna. The primary efficacy parameter was chosen similarly for the two trials. For the US study, the incidence of hematuria was measured and significant hematuria was defined as > 50 rbc/hpf. For the German study, the primary efficacy parameter was defined as the maximum number of RBCs/µl of urine based on FRC photo-counting over Days 2-10.

The US study is a crossover study where patients were treated for two ifosfamide chemotherapy cycles. Mesna treatment was randomized so that in one cycle patients received the standard iv treatment and in the other cycle patients received the iv plus oral dosing regimen with Mesna tablets. Enrollment of **120 patients** over 8 centers in the US was planned in the protocol for the US study. The sample size calculation for the US study was based on equivalence. The two regimens were to be considered equivalent if the (two-sided) 95%-confidence bound for the **absolute** difference d=p1-p2, where p1 and p2 are the probabilities of observing a severe microhematuria or a macrohematuria with the iv+po regimen and the iv regimen respectively, was less than **10%. There was no interim analysis planned in the protocol.**

The European study utilized a parallel design, where patients were randomized to one of the two treatments and were studied for one cycle only. Levels of hematuria were measured by counting red blood cells in the urine. In the European study a more sensitive method (FRC) of measuring hematuria was used. Using this system, rbc/µl are measured in fresh urine. The primary parameter of uroprotective efficacy was defined as the maximum number of RBCs/µl of urine detected during the last 4 days of a 5-day ifosfamide regimen and 5 days of post-treatment follow-up. A difference of 100 RBCs/µl (10RBCs/hpf) between the approved iv/iv/iv regimen and the experimental iv/po/po regimen was chosen as the criterion used to differentiate the two study drug regimens. The uroprotective efficacy of the two regimens was to be considered equivalent if the maximum number of urinary RBCs

observed with the iv/po/po regimen was at least comparable to that observed with the iv/iv/iv regimen, allowing for a difference of up to 100 RBCs/µl (=10 RBCs/hpf) with respect to the shift of the primary parameter of uroprotective efficacy between the iv/iv/iv and iv/po/po regimens. Statistical comparison of the two treatment arms was performed using one-sided tests. One interim analysis was planned for the sample size re-estimation, hence, no adjustment for the type I error was considered. A total of 54 patients were recruited and randomized to treatment with either the iv/iv/iv regimen (n=27) or the iv/po/po regimen (n=27). No details in the sample size calculation were provided about the power of this study.

By the end of September 1996, there were 66 out of the 120 patients enrolled in the US study. Due to this low recruitment for the US study, with the consent of FDA (August, 1996), the sponsor submitted the NDA with the German study (MED 504) as the primary demonstration of efficacy of the iv plus oral dosing regimen of Mesna, with confirmation from the US data that the iv plus oral dose schedule is not worse than the iv schedule and better than the administration of ifosfamide without Mesna. All 66 patients entered in the study were included in the intent-to-treat analysis. A total of 27 patients (Mesna iv+po/iv: n=13; Mesna iv/iv+po: n=14) were excluded from the per-protocol analysis and included only in the intent-to-treat analysis. Thus, 20 patients in the Mesna iv+po/iv sequence and 19 patients in the Mesna iv/iv+po sequence were included in the per-protocol analysis.

III. Summary of Efficacy Results and Reviewer's Comments

Study MR9205002A (US)

Two study populations were defined for the statistical analyses planned in the protocol. The intent-to-treat population consisted of all patients who **received at least one dose of Mesna.** The per-protocol-population consisted all patients who were evaluable for hematuria (for definition see Vol. 1.62, page 24). The primary endpoint was the rate of severe hematuria, i.e., number of RBCs/hpf > 50 (1 RBCs/hpf = 10 RBCs/µl) or visible blood. An upper 95% confidence bound was to be estimated based on the normal approximation of the absolute difference d=p1-p2 where p1 and p2 are the proportions of observing a severe microhematuria or visible blood with the iv+po and iv regimens, respectively. A total of 66 patients were recruited and randomized to treatment with sequence 1 (Mesna iv+po/iv; n=33) or with sequence 2 (Mesna iv/iv+po; n=33). All patients randomized received at least one dose of Mesna. Of these, 17 patients were discontinued prematurely (iv+po/iv group: n=9; iv/iv+po: n=8). Reasons for the

discontiuation are summarized in the following Reviewer's Table 1.

Reviewer's Table 1. Patients Discontinued Prematurely Reasons for Discontiuation, US study

	iv+po/iv	iv/iv+po
Death	5	0
Other reasons	4	8

Reviewer's Comments:

- According to Reviewer's Table 1, the reason for discontinuation (death vs other reasons) is significantly associated with the assignment of the treatment sequence (Fisher's Exact test, **p=0.029**).
- If death is counted as failure, the patients treated in the Mesna iv+po/iv sequence had significantly (**p=0.053**, Fisher's exact test; **p=0.022**, Chi-square asymptotic test) higher rate of death than those treated in the Mesna iv/iv+po sequence. The results are summarized in the following Reviewer's Table 2.

Reviewer's Table 2. Patients Discontinued Prematurely Breakdown by Deaths, US study

	iv+po/iv	iv/iv+po
Survival	28	33
Death	5	0

Based on the sponsor's memorandum (9/12/97), the number of patients treated by sequence and cycle and incidence of treatment failures (hematuria) are summarized as follows in Reviewer's Table 3.

Reviewer's Table 3. Incidence of Treatment Failure Related to Number of patients Treated, US study

	Severe Hematuria Rate	
Treatment Sequence	Cycle 1	Cycle 2
iv+po/iv	1/33 (3%)	1/25(4%)
iv/iv+po	0/33 (0%)	0/27(0%)

The sponsor's 95% Upper confidence bounds of the difference of

incidence of hematuria were calculated based on their "intent-to-treat" population and their per protocol population (the two cycle cross-over data). The sponsor's results are presented in the following Reviewer's Table 4.

Reviewer's Table 4. Comparison of the Incidence of Grade III or IV Hematuria Observed with Mesna iv+po and Mesna iv Regimens- Intent-to-treat and Per-Protocol Populations, US Study

Analysis	Incidence of Grade III or IV Hematuria		Difference	95% Upper Confidence bound (one-sided)
	iv+po	iv		
Intent-to-treat	1/60=1.7%	1/58=1.7%	-*	-*
Per protocol	1/39=2.6%	1/39=2.6%	0.0%	6.0%

* not provided by the sponsor.

Reviewer's Comments:

- The sponsor only provided one-sided 95% confidence bound for the per-protocol analysis. The two-sided 95% confidence interval for the estimate of the upper confidence bound is slightly high (7%), which still demonstrates equivalence of the two regimens.

In the intent-to-treat analysis the sponsor included those patients *who received at least one dose of Mesna and counted all patients who dropped from the second cycle of the study as successes.*

Reviewer's Comments:

- Intent-to-treat population should include all patients as randomized (iv arm: 33 patients, iv+po arm: 33 patients) not just those who "*received at least one dose of Mesna" (iv arm: 27 patients, iv+po arm: 19 patients).*
- According to intent-to-treat criterion, patients who dropped from the study should be counted as failures not successes. However, in the sponsor's cross-over analysis (using the two cycle data) those patients who dropped in the second cycle were counted as "successes."
- Due to the loss of over 15% of patients in the second cycle of the study, the analyses based on the cross-over data may not be valid. With so many missing subjects, the major issue of such analyses is as pointed out in the ICH guideline that "*There are additional problems that need careful attention in*

the cross-over trials. The most notable of these are the ***complications of analysis and interpretation*** *arising from the loss of subjects."* Since most patients completed the first cycle study, this reviewer suggests conducting the statistical analysis based on the first cycle data only (using parallel comparison). The result is presented in the following Reviewer's Table

Reviewer's Table 5. Result of Two Sample Comparison Based on the First Cycle Data, US study*

Incidence of Grade III or IV Hematuria		Difference	95% CI one-sided	95% CI two-sided
iv+po	iv			
1/33=3%	1/33=3%	0%	(-9.9%, 9.9%)	(-11.3%,11.3%)

* The analysis includes all patients who have records in the first cycle study. Those patients who discontinued prematurely were counted "success" if no events were observed.

The result demonstrates a marginal equivalence of the two treatment regimens.

Study MED504 (German)

This was a Phase III, multicenter, randomized, parallel group study designed to evaluate the uroprotective efficacy and safety of iv/iv/iv and iv/po/po Mesna regimens in cancer patients receiving treatment with ifosfamide 2.0 g/m^2/day for 5 consecutive days, with a 17-day post treatment follow-up period. A total of 54 (Mesna iv/iv/iv, n=28; iv/po/po, n=26) patients were enrolled in the study. Of these, two patients, both randomized to the iv/po/po regimen, did not receive study drug and four patients were discontinued prematurely from the study. Two patients (one iv/po/po patient and one iv/iv/iv patient) died from progressive disease after receiving the second dose of ifosfamide. One iv/iv/iv patient withdrew his consent to participate in the study after day 5 and chemotherapy had to be stopped for an iv/iv/iv patient due to severe leukopenia. Fifty two patients (Mesna iv/iv/iv: n=27; Mesna iv/po/po: n=25) who received at least one dose of study drug were included in the intent-to-treat analysis. However, for the primary efficacy parameter, two patients in the iv/po/po group were excluded because all photo-counts were missing. Fifteen patients (Mesna iv/iv/iv: n=9; Mesna iv/po/po: n=6) were excluded from the per-protocol analysis and included only in the intent to-treat analysis. Thus, 18 patients in the iv/iv/iv group and 19 patients

in the iv/po/po group were included in the per-protocol analysis. Efficacy analysis was performed for both the intent-to-treat and per-protocol analysis populations. The per-protocol analysis for the primary parameter of efficacy was regarded as the confirmatory analyses.

The therapeutic equivalence of the two Mesna regimens with respect to their effect on the primary efficacy parameter (the maximum number of RBCs/µl of urine) was to be tested with a one-sided exact Wilcoxon rank sum test. The Hodges-Lehmann estimator was calculated as an estimator for the shift parameter of the distribution. An upper 95% confidence limit of a two-sided confidence interval was calculated. The two regimens are considered to be equivalent in efficacy, if the efficacy of the iv/po/po regimen was not worse than 100 RBCs/ul compared to the efficacy of the iv/iv/iv regimen.

The sponsor's results are summarized in the following Reviewer's Table 6.

Reviewer's Table 6. Between-Group Comparisons of Maximum RBCs/µl Counts by FRC Photo-count Method, German Study

	Population		Difference (RBCs/µl)	95% CI two-sided (RBCs/µl)
	iv	po		
intent-to-treat	27	23	0.0	(-11,8)
per-protocol	18	19	3.0	(-11,14)

The p-values of one-sided Wilcoxon-Mann-Whitney test for both intent-to-treat and per-protocol populations are 0.0001, which indicates that the difference in RBC counts between the two treatment groups was significantly lower than 100 RBCs/µl.

Reviewer's Comments

- As pointed out above, Intent-to-treat population should include all patients as randomized (iv arm: 28 patients, iv+po arm: 26 patients) not just those who "*received at least one dose of Mesna" (iv arm: 27 patients, iv+po arm: 23 patients).*

- (Validation Report) In this study, a Fuchs-Rosenthal-Chamber (FRC) was used to count red blood cells (RBCs) in the uncentrifuged urine. The accuracy of the method was examined by the sponsor. The sponsor states in the validation study of the FRC method that *"The precision of the method in terms of*

the mean deviation from the target concentration is less than or close to 10%, which is an acceptable variability. ***The only exceptions are the C.V. for the measurement at the lowest concentrations (i.e. 5 and 15 RBCs/ul).*** Based on the sponsor's report, this method losses the precision if the concentration is lower, i.e., the measurement error is too large. It is questionable for the sponsor to consider the urine RBC concentration as a continuous biometrical parameter because the maximum numbers of RBCs/ul for about half of the patients in this study were small (**28 pts : < 20 RBCs/ul, 20 pts: < 15 RBCs/ul**) Thus, the statistical hypotheses and procedures used in the study are not valid due to the impact of large measurement errors.

- A one-sided test is inappropriate. Two-sided tests and confidence intervals should be used in the study.

- Two methods were used in handling the missing data in the trial. In the primary analysis, the missing data were excluded and for the secondary analysis two imputation methods were used: 1) the last observation carried forward (LOCF) method, and 2) the regression parameter was used to calculate the sum of the photo-counts based on the sum of the direct microscopic counts. Validity of both methods was based on the assumption that data are "missing at random", which may not be true. If there is an indication of nonrandom missing mechanism, imputing missing data has the potential for bias.

- The RBC count in a urine sample might be dependent on daily fluid intake. Higher daily fluid intake may cause a lower RBC count. The sponsor examined the **mean** fluid intakes and **means** of specific gravity of urine samples in the two groups and claimed that "*no difference between the two mesna treatment groups in the amount of hydration or the number and type of deviations was observed,*" and that " *the measured urinary RBC concentrations have not unevenly been diluted by diuresis.*" However, due to the primary parameter used for the comparison of the maximum number of RBCs/ul, the reasons the sponsor provided above do not appear adequate to explain the direct relationship between hydration and the RBC concentration.

- As done in the US study, the frequency of hematuria grades is a more reliable parameter than the RBC count to demonstrate the efficacy of the therapy. The sponsor's results based on the frequencies of hematuria grades are summarized in the following Reviewer's table 7.

Reviewer's Table 7. Frequencies of Hematuria Grades for Intent-to-Treat and Per Protocol Populations, German Study

RBC count(RBCs/µl) maximum over Days 2-10	<50	≥50
	Intent-to-treat	
Mesna iv/iv/iv	21	6
Mesna iv/po/po	22	1
	Per-Protocol	
Mesna iv/iv/iv	14	4
Mesna iv/po/po	18	1

In the intent-to-treat and per-protocol populations, 22% of patients in the iv/iv/iv group and 5% of patients in the iv/po/po group had maximum RBC counts in urine over 50 RBCs/ul (abnormal level). This reviewer conducted a Fisher's Exact test for both populations. The following Reviewer's Table shows that the Mesna iv/iv/iv and iv/po/po regimens were equally effective.

Reviewer's Table 8. Confidence Intervals for Frequencies of Hematuria Event (Level III +) Intent-to-Treat and Per Protocol Populations, German Study

	Difference Hematuria Frequency % of iv/po/po - % of iv/iv/iv	95% Two-Sided Confidence Interval & p-value
Intent-to-Treat iv/po/po vs iv/iv/iv	1/23-6/27=-18%	(-40%, 4%) p=0.11*
Per Protocol iv/po/po vs iv/iv/iv	1/19-4/18=-17%	(-44%, 10%) p=0.18*

* Smaller p-value indicates that iv/po/po regimen has better protective effect.

IV. Overall Summary and Conclusions:

Summary:

The trials, **MR9205002A** and **MED504**, were designed to show that the Mesna iv/po/po regimen and iv/iv/iv regimen were equally effective in protecting patients from ifosfamide-induced urotoxicity. These two trials were reviewed for statistical design and efficacy analysis findings. This reviewer's

conclusions are summarized as follows.

- For the US study (**MR9205002A**), both the sponsor's intent-to-treat analysis and per protocol analysis showed that both Mesna iv/iv/iv and iv/po/po regimens are equally protective. Due to a higher percentage of loss of subjects, the analyses used by the sponsor based on the cross-over trial data was questionable. This reviewer conducted a parallel (between group) comparison using only the first cycle data. The reviewer's results showed that the **one-sided 95%** upper confidence limit for the difference in severe hematuria rates between the two regimens was 9.9% (**11.3% for the two-sided 95% CI**). The upper bound of the two-sided 95% confidence interval is slightly higher than the upper confidence bound of 10% defined for the equivalence of the two regimens in the protocol.

- For the US study, the patients treated on the Mesna iv+po/iv sequence had statistically significantly higher rate of death than those treated on the Mesna iv/iv+po sequence (**p=0.053**, exact test, **p=0.022**, asymptotic test, Reviewer's Tables 1 & 2). The sponsor needs to investigate further whether death is associated with the use of Mesna oral drug.

- For the German study (MED504), the sponsor selected the maximum number of RBCs instead of hematuria grades as the primary efficacy endpoint. A two-sided confidence interval for difference of (-11,8) (intent-to-treat) demonstrates therapeutic equivalence of the two Mesna regimens. Due to the limitation of the FRC method, lower RBC counts could not be detected accurately, i.e. the data were truncated at RBC count = 20 RBCs/µl. In this case, frequency is a better parameter to evaluate the efficacy of the therapy. Using the frequencies of the patients who had RBC count > 50 RBCs/ul > 50 in the two arms, the results (Reviewer's Table 10) demonstrated that the protective efficacy of the Mesna iv/po/po regimen is not inferior to that of the Mesna iv/iv/iv regimen (two-sided 95% CI: (-40%,4%), intent-to-treat population).

Conclusion:

Results of the sponsor's and this reviewer's analyses based on the sponsor's data for the German study indicated that the Mesna iv/iv/iv and iv/po/po regimens were equally effective in protecting patients from ifosfamide-induced urotoxicity. The US study also provided a supportive evidence of the equivalence of the two regimens.

Addendum #1

This Addendum addresses the influence of the exclusion of 12 patients in Center #5 (inadequate data collection) on the efficacy results.

According the FDA's audit of the study centers, data collected in study center #5 were inadequate. The influence of the exclusion of 12 patients in center 5 on efficacy results is investigated in this review. The results are summarized below.

All patients but one recruited in center 5 were actually excluded from the sponsor's per protocol analysis in the way the sponsor used to calculate the confidence bound for the equivalence of the two regimens (based on the cross-over data). Therefore, exclusion of the data from center 5 has no influence on the sponsor's results obtained using the cross-over data. The results are summarized in the following Table.

Reviewer's Table 1. Comparison of the Incidence of Grade III or IV Hematuria Observed with Mesna iv+po and Mesna iv Regimens, US Study Center 5 Excluded

Analysis	Incidence of Grade III or IV Hematuria		Difference	95% Upper Confidence bound one-sided
	iv+po	iv		
Per protocol	1/38=2.6%	1/38=2.6%	0.0%	6.0%

Reviewer's Comments:

Due to the loss of over 15% of patients in the second cycle of the study, the analyses based on the cross-over data may not be valid. In this circumstance, comparison based on the first cycle data is more reliable. We simply performed an "intent-to-treat" analysis based on the first cycle data **excluding all patients recruited in center 5**. Only one severe hematuria in the iv+po group (patient [redacted] Center 3) was identified in the first cycle of the study. In this "intent-to-treat" analysis, those patients who discontinued prematurely were counted as "success" (if no event was observed) even though this may be optimistic (it may underestimate the rate of the events). The result indicates that the upper confidence limit of the estimated difference in

hematuria rates is about **15%**. If we exclude those patients who discontinued prematurely, the upper confidence limit will be obviously higher than 15% due to inflation of the standard error. For example, if we exclude the 5 patients who had protocol violation (3 in the iv+po group and 2 in the iv group) from the analysis, the upper confidence limit is as high as **17%**. Of these 5 patients, 2 iv+po patients received the iv schedule during the treatment regimen and 1 iv+po patient had hydration > 6 l per day; both iv patients had a dose of ifosfamide < 4.5 g/m2 per cycle. The confidence intervals are summarized in the following table.

Reviewer's Table 2. Result of Two Sample Comparison Based on the First Cycle Data, US study Center 5 Excluded

	Incidence of Grade III or IV Hematuria		Difference	95% Upper Confidence Bound (one-sided)
	iv+po	iv		
"Per Protocol"	**1/21=4.8%**	**0/23=0**	**4.8%**	**17%**
"Intent-to-Treat"	**1/24=4.2%**	**0/25=0**	**4.2%**	**15%**

The results indicate that the upper confidence limits of an one-sided confidence interval are substantially greater than 10% and thus fail to demonstrate that the two treatment regimens are equivalent.

APPEARS THIS WAY ON ORIGINAL

Addendum #2

This Addendum reviews the sponsor's amended report (Vol. B2, Submission dated 12/17/97) of the original NDA submission for Mesna. In this report, the sponsor has updated their efficacy analyses because 5 additional patients (4 in iv/iv+po arm and 1 in iv+po/iv arm, one iv/iv+po patient from Center #5) have been entered into the study since the interim analysis of this study. The sponsor acknowledged in the report that *"During a June 1997 audit of one of the study sites, Center #5, C. Julian Rosenthal, MD, a number of issues were raised. For many of the patients adequate records of the conduct of the required urinalysis measurements were not kept. In addition, concomitant medications and adverse events were not always accurately recorded. In some patients, data were included for non-study cycles of chemotherapy and not recorded for study related cycles."*

The influence of the exclusion of 12 patients in center #5 on the efficacy results has been investigated in this reviewer's Statistical Review Addendum #1. With the inclusion of 5 additional patients, the sponsor reconducted the analyses using 1) only data from cycle one; and 2) data from the both cycles (cross-over study).

The sponsor first reanalyzed the data for the primary efficacy endpoint (occurrence of severe microhematuria, > 50 RBCs/hpf) using cycle one data for the **71 patients** who participated in the study (**including 12 patients of center #5**). The sponsor's results, presented in the following Reviewer's Table, showed that the upper 95% confidence bound (using Yates' correction) was 10.5% *"which is slightly above the equivalence range specified in the protocol (10%)."*

Reviewer's Table 1. Comparison of the Incidence of Grade III or IV Hematuria Observed with Mesna iv+po and Mesna iv Regimens in First Cycle, US Study, Center 5 Included

Analysis	Incidence of Hematuria iv+po	iv	Diff.	95% Upper Confidence bound two-sided	95% Upper Confidence bound one-sided
Intent-to-treat	1/34=2.9%	0/37=0%	2.9%	**11.4%**	**10.5%**

Reviewer's Comments: Patients enrolled in Center #5 should be excluded from the analysis. Then the total number of valid patients will be **59** (66-12+5=59). The difference of the incidences and associated confidence bound based on these 59 patients are summarized in the following Reviewer's Table.

Reviewer's Table 2. Comparison of the Incidence of Grade III or IV Hematuria Observed with Mesna iv+po and Mesna iv Regimens in First Cycle, US Study, Center 5 Excluded

Analysis	Incidence of Hematuria		Diff.	95% CI two-sided	95% CI one-sided
	iv+po	iv			
Intent-to-treat*	**1/25=4%**	**0/29=0**	**4%**	(-7.4%, **15.4%**)	(-6.2%, **14.1%**)

* *Based on the sponsor's definition, the intent-to-treat population included patients who received some treatment.*

The results indicate that the upper confidence limits are substantially greater than 10% and thus fail to demonstrate that the two treatment regimens are equivalent.

In the second part of this report the sponsor conducted the analyses using the both cycle data without the inclusion of those patients enrolled in Center #5. The sponsor stated in the report that "*The results of both statistical analyses (with Center #5 and without Center #5) show that there was no difference between the proposed mesna iv+po regimen and the approved iv regimen with respect to the incidence of Grade III or Grade IV hematuria.*" As pointed out in this reviewer's Review Addendum #1, since all patients but one recruited in center 5 were actually excluded from the sponsor's per protocol analysis, the exclusion of data from center 5 has no influence on the results obtained by the sponsor. However, due to the loss of over 15% of patients in the second cycle of the study, the analyses based on the cross-over data may not be valid. On the other hand, if the sponsor would like to use the cross-over data in the intent-to-treat analysis, those patients with missing data in the second cycle should be counted to be failures (events) based on the intent-to-treat criterion. However, in the sponsor's analyses, those patients were used as successes. The estimates and associated confidence intervals based on these data may not be reliable.

Overall Conclusions

Results of the sponsor's and this reviewer's analyses, based on the sponsor's data for the German study, indicated that the Mesna iv/iv/iv and iv/po/po regimens were equally effective in protecting patients from ifosfamide-induced urotoxicity. However, the US study, due to the exclusion of 12 patients treated in Center #5 (inadequate data collection), did not provide sufficiently supportive evidence of the equivalence of the two regimens.

/S/

Gang Chen, Ph.D.
Mathematical Statistician

Concur: Dr. T. Koutsoukos /S/ 2/27/98

Dr. G. Chi /S/ 3/3/98

CC:

Orig. NDA 20-855
HFD-150/ ~~Ms. Vaccari~~ Mr. Quinn, CSO
HFD-150/ Dr. Beitz
HFD-150/ Dr. Sokol
HFD-344/ Dr. Barton
HFD-710/ Dr. Chi
HFD-710/ Dr. Koutsoukos
HFD-710/ Dr. Chen
HFD-710/Chron

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This review consists of 16 pages of text.

Vaccari

MAY 15 1997

Memo

45 Day meeting overview / Statistics

NDA#: 20-855

Applicant: ASTA Medica, Inc., Hackensack, New Jersey

Name of Drug: Mesna Tablets

Indication: Prevention of Ifosfamide-induced Hemorrhagic cystitis

Documents Reviewed: Vol. .1 .58 .59

Medical Officer: Gerald Sokol M.D.

The statistical sections of the application are complete and well organized. Results of the two multicenter controlled trials, study D-07093-0018 (MR9205002A, USA study) and study MEND504 (Germany study) are reported. Study D-07093-0018 is an open label two-way crossover trial comparing the treatment iv + po/iv with iv/iv+po. Study MEND504 is an open-label, parallel group study conducted in Germany comparing the treatment iv/iv/iv with iv/po/po. The sponsor has responded to this reviewer's questions concerning the SAS programs. The SAS programming codes were clarified by the sponsor for the two controlled studies and the SAS data sets are available.

This application is sufficiently complete for statistical review and is filable from a statistical standpoint.

/S/

Gang Chen, Ph.D.
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Orig. NDA 20-855/DIV FILE
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HFD-150/ Dr. Beitz
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HFD-710/ Dr. Gnecco
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